UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF OHIO
EASTERN DIVISION

IN RE NATIONAL PRESCRIPTION OPIATE LITIGATION **This document relates to**: *Track Three Cases*	**MDL No. 2804** **Case No. 17-md-2804** **Judge Dan Aaron Polster**

MEMORANDUM IN SUPPORT OF DEFENDANTS' MOTION TO EXCLUDE CERTAIN OPINIONS AND TESTIMONY OF DR. KATHERINE KEYES

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INTRODUCTION

Defendants[1] respectfully move to exclude certain opinions and testimony of Plaintiffs' expert, Dr. Katherine Keyes, because they are unreliable and inadmissible.

First, Defendants seek to exclude Dr. Keyes' marketing testimony and opinions as to Defendants. This Court and Judge Faber already excluded substantively identical opinions in Tracks One and Two. ECF No. 2549; Ex. 8. This Court should do the same here, for the reasons it did so previously and for additional reasons specific to Defendants here—namely, that Dr. Keyes' methodology is flawed as to Defendants, and any such opinions would be misleading, confusing, and unfairly prejudicial.

Second, Defendants move to exclude Dr. Keyes' testimony and opinions that "prescription opioid use is also responsible for the increase in fentanyl and other synthetic opioid harms," Ex. 1 at 39, her "estimate that approximately 70–80% of fentanyl-involved opioid deaths are attributable to prescription opioid use," *id.*, and her so-called "conservative . . . approach to estimating the proportion of OUD [Opioid Use Disorder] cases and deaths for which prescription opioids were not listed as a contributing factor that are indirectly attributable to prescription opioids in Ohio and Lake and Trumbull Counties," *id.* at 59–61. Those opinions—which she has never advanced outside the courtroom, are not based on peer-reviewed literature, and have not been scientifically tested in any way—are solely the product of Dr. Keyes' unsound reasoning, not any reliable scientific methodology. Because these opinions, which even Dr. Keyes acknowledges are merely "estimates," are "connected to existing data only by the *ipse dixit* of the expert," *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997), the Court should exclude them.

[1] CVS Indiana, L.L.C., CVS Rx Services, Inc., CVS Pharmacy, Inc., CVS TN Distribution, L.L.C., Ohio CVS Stores, L.L.C., Giant Eagle, HBC Service Company, Walmart Inc., Rite Aid Hdqtrs. Corp., Rite Aid of Ohio, Inc., Rite Aid of Maryland, Inc. d/b/a Right Aid Mid-Atlantic Customer Support Center, Eckerd Corp. d/b/a Rite Aid Liverpool Distribution Center, Walgreens Boots Alliance, Inc., Walgreen Co., and Walgreen Eastern Co., Inc.

Third, the Court should exclude Dr. Keyes' testimony and opinions regarding causation—or at least limit them with an instruction that her definition differs from legal causation[2]—because they will mislead and confuse the jury, causing unfair prejudice to the Defendants. While these shortcomings apply to Dr. Keyes' overall causation methodology (where she concludes that causation is established "if some cases would not have occurred in the absence of prescription opioid use")[3] and conclusions, they are particularly well-illustrated by her flawed attempts to attribute to prescription opioids the harms caused by drug dealers' relatively recent introduction of illicit and highly potent synthetic opioids into the illegal drug supply.

LEGAL STANDARD

Expert evidence "can be both powerful and quite misleading because of the difficulty in evaluating it." *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 595 (1993). Federal district courts therefore have been assigned a gatekeeping function to exclude expert evidence that "is unreliable and irrelevant" under Federal Rule of Evidence 702. *Id.* at 597; *Conwood Co. v. U.S. Tobacco Co.*, 290 F.3d 768, 792 (6th Cir. 2002).

Rule 702 in turn has three requirements: (1) the witness must be qualified; (2) the witness' testimony must be helpful to the fact-finder in resolving relevant issues; and (3) the witness' testimony must be reliable. *In re Scrap Metal Antitrust Litig.*, 527 F.3d 517, 529 (6th Cir. 2008); *Saint Gobain Autover USA, Inc. v. Xinyi Glass N. Am., Inc.*, 666 F. Supp. 2d 820, 830 (N.D. Ohio

[2] This Court has previously permitted testimony by Dr. Keyes regarding the "gateway" hypothesis, stating that Dr. Keyes used an acceptable methodology and such testimony was "neither methodologically illegitimate nor fundamentally misleading." ECF. No. 2518. Defendants preserve their prior objection to such testimony. If testimony about this hypothesis is admitted, however, it is all the more important that the jury not be misled to equate the Bradford Hill "viewpoints" with the legal standard of causation. Testimony about "causation" or terminology that will be understood as assigning causal responsibility unsupported by reliable science must be excluded. To the extent Dr. Keyes is allowed to testify to "causation" at trial, Defendants reserve the right to propose a curative jury instruction to be read following her testimony, as her concept of causation differs, in important ways, from the determination of legal causation that belongs to the jury, and on which only the Court may instruct the jury.

[3] Ex. 1 at 11.

2009). These requirements apply to all expert testimony. *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 147 (1999) (stating that Rule 702 makes "no relevant distinction between 'scientific' knowledge and 'technical' or 'other specialized' knowledge").

Rule 702 provides general standards for courts to assess reliability. First, the testimony must be based upon "sufficient facts or data." Fed. R. Evid. 702. Second, the testimony must be the "product of reliable principles and methods." *Id.* Third, the expert must have "reliably applied the principles and methods to the facts of the case." *Id.* In assessing reliability, courts in this Circuit can rely upon any number of the non-exhaustive list of factors identified by the Supreme Court in *Daubert*, including: (1) whether a theory or technique has been or can be tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) the known or potential rate of error of the method used and existence and maintenance of standards controlling the technique's operation; and (4) whether the theory or method has been generally accepted by the scientific community. *United States v. Langan*, 263 F.3d 613, 621 (6th Cir. 2001) (citing *Daubert*, 509 U.S. at 593–94); *see also Nelson v. Tenn. Gas Pipeline Co.*, 243 F.3d 244, 251 (6th Cir. 2001) (providing that the *Daubert* factors will often be appropriate in determining reliability).

The general gatekeeping obligation set forth in *Daubert* applies when considering all expert testimony, including testimony based on technical and other specialized knowledge. *Clay v. Ford Motor Co.*, 215 F.3d 663, 667 (6th Cir. 2000) (citing *Kumho Tire*, 526 U.S. at 141). District courts have "considerable leeway in deciding in a particular case how to go about determining whether particular expert testimony is reliable." *Madej v. Maiden*, 951 F.3d 364, 374 (6th Cir.), *cert. denied*, 141 S. Ct. 612 (2020) (citing *Kumho Tire*, 526 U.S. at 152). A district court is not required to admit expert testimony "that is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion

proffered." *Nelson*, 243 F.3d at 254. The Court also must exercise its discretion to determine "whether the testimony will assist the fact-finder" in deciding the issues presented. *Fox v. Van Dorn Demag Corp.*, No. 5:08 CV 1668, 2009 WL 10689996, at *2 (N.D. Ohio Sept. 8, 2009).

ARGUMENT

I. THE COURT SHOULD EXCLUDE DR. KEYES' MARKETING OPINIONS AS TO DEFENDANTS.

In her Track Three report, Dr. Keyes, an epidemiologist, offers the following opinions regarding marketing:

- "The increase in opioid prescribing was driven by a multitude of factors, including direct marketing to physicians using data that underestimated the opioid use disorder risk in patients, which I will detail in Section B. Evidence shows that pharmaceutical marketing of prescription drugs increases prescribers' likelihood of prescribing the marketed drugs in the future. That is also true for prescription opioids; as a result, increasing marketing of opioid drugs led to increased sales of the marketed drugs." Ex. 1 at 14 (citations omitted).

- "The supply of opioids was also facilitated by pharmaceutical promotional activity to physicians. While I did not evaluate ***the specific materials of the manufacturers***, I did evaluate peer-reviewed epidemiological studies that document the association between opioid marketing with sales, which is germane to my expertise." Ex. 1 at 33 (emphasis added).

In her Track Three deposition, Dr. Keyes acknowledges that her report set out all of her opinions for purposes of Federal Rule of Civil Procedure 26(a)(2)(B)(i). Ex. 5 at 17:15-19:19. These opinions are substantively identical to ones she offered in Tracks One and Two. Ex. 2 at 10-11 & 22; Ex. 3 at 14 & 29–30. Although Dr. Keyes purports to be offering these opinions against Defendants in Track Three, her report never mentions any Defendant and she acknowledges she does not have "any specific opinions about CVS [or the other Defendants] uniquely," Ex. 5 at 26:3–7, 27:16–28:8; she reviewed no materials produced by Defendants, *id.* at 26:3–15; she reviewed no testimony provided by Defendants' employees, *id.* at 26:16–22; she conducted no analysis of what, if anything, prescribers in Lake and Trumbull Counties saw and/or relied upon

in making prescribing decisions, *id.* at 91:19–92:18; and she previously testified correctly that the articles that she reviewed to support her marketing opinions in this case relate to entities other than the chain pharmacies, Ex. 6 at 149:10–15. Despite her previous testimony, at her Track Three deposition, Dr. Keyes refused to acknowledge that her marketing opinions related to manufacturers, not Defendants. Instead, she speculated that the phrase "pharmaceutical companies" in an article could be read to include Defendants. Ex. 5 at 82:13–18. To be sure, she could not recall any article she relied on mentioning any marketing by any pharmacy. *Id.* at 90:6–10.[4] And, on direct examination in the New York *Frye* Hearing, by contrast, she previously testified that this same article was about manufacturers. Ex. 6 at 104:25–105:5 (testifying that the article "found an association between the amount of money that doctors received from *opioid manufacturers* with subsequent opioid prescribing") (emphasis added).

This Court excluded Dr. Keyes' marketing causation opinions in Track One. ECF No. 2549. Judge Faber did the same in Track Two. Ex. 8.[5] The Court should preclude Dr. Keyes' attempt to extend her marketing opinions to Defendants in Track Three as well, under *Daubert*, 509 U.S. 579, and Rules 402, 403, and 702 of the Federal Rules of Evidence, for the following reasons: (a) she is not qualified to offer her marketing opinions, as this Court and Judge Faber

[4] *See also id.* at 103:23–104: 22 (Q. Let's start on Page 14, "direct marketing to physicians." Are you aware of any activities by pharmacies that entail direct marketing to physicians . . . . A. That goes back to the Hadland article and the testimony I have already provided about the Open Payments database. Q. Okay. So—and your testimony was that you don't know one way or another whether that relates to pharmacies? A. We can go back and read the testimony. I mean, I didn't say I don't know one way or the other. What I said was the Hadland article is based on the Open Payments databases, and that what is reported in the Methods section is that pharmaceutical companies are in the Open Payments database. I have not analyzed the Open Payments database to derive what industry each company that is in the Open Payments database is from.").

[5] The defendants also challenged Dr. Keyes' marketing opinions in New York. While the New York Court's written decision did not explicitly exclude any of Dr. Keyes' opinions, that decision did not list marketing causation as an issue raised by the defendants and did not address those arguments. Ex. 9 at 17–20. Moreover, in a footnote to the section of the decision concerning Dr. Lembke that immediately precedes the section on Dr. Keyes, the Court sustained an objection to marketing causation. *Id.* at 16 n.8. It is unclear whether that reference applied only to Dr. Lembke's opinions or to marketing causation opinions offered by other experts as well.

previously held; (b) she did not apply a reliable methodology; (c) her opinions do not "fit" this case; and (d) unless her marketing opinions are specifically limited to entities other than Defendants, they are misleading, confusing, and unfairly prejudicial.

Because Dr. Keyes' report does not set forth any opinions concerning the effects of marketing by any Defendants, any such undisclosed opinions would be inadmissible. While Plaintiffs may not intend to offer any such opinions, Dr. Keyes' unwillingness to limit her opinions about the effect of marketing in her deposition necessitates this Motion.

A. Dr. Keyes is Not Qualified to Offer Marketing Opinions.

As this Court and Judge Faber held, Dr. Keyes is not qualified to offer her marketing opinions. ECF No. 2549; Ex. 8; *see also* ECF No. 1868-2 at 3 & 5–6 (discussing Dr. Keyes' lack of qualifications to offer marketing causation opinions and citing cases in support of exclusion); ECF No. 2479 at 3. Dr. Keyes' qualifications have not changed, and this Court should once again exclude her opinions about marketing.[6]

B. Dr. Keyes' Methodology is Unreliable and Fails as to Defendants.

Dr. Keyes' report does not identify any marketing by any Defendant in this case that she contends had any effect on prescribing practices. That is enough to exclude an opinion that is not based on evidence.

Dr. Keyes also failed to apply a reliable methodology to determine whether marketing by Defendants had any effect on prescribing practices. She did not review *any* documents or testimony provided by Defendants in this case. Ex. 5 at 26:3–22. She did not evaluate any

[6] *See, e.g.*, *Rheinfrank v. Abott Labs., Inc.*, No. 1:13-CV-144, 2015 WL 13022172, at *11 (S.D. Ohio Oct. 2, 2015), *aff'd*, 680 F. App'x 369 (6th Cir. 2017); *Pfizer Inc. v. Teva Pharms. USA, Inc.*, 461 F. Supp. 2d 271, 276 (D.N.J. 2006); *Popovich v. Sony Music Entm't, Inc.*, No. 1:02 CV 359, 2005 WL 5990223, at *3 (N.D. Ohio May 9, 2005); *Chem. Solvents, Inc. v. Advantage Eng'g, Inc.*, No. 1:10-CV-01902, 2011 WL 1326034, at *7 (N.D. Ohio Apr. 6, 2011) (same); *In re Prempro Prods. Liab. Litig.*, 554 F. Supp. 2d 871, 884 (E.D. Ark. 2008), *aff'd*, 586 F.3d 547, 571 (8th Cir. 2009).

prescribers and, therefore, did not know what caused any particular prescriber to write a particular prescription, or whether any prescriber ever "saw marketing materials." *Id.* at 91:19–92:13. In fact, Dr. Keyes conducted no analysis specific to marketing directed to prescribers in Lake and Trumbull Counties. *Id.* at 92:14–18; *see also* ECF No. 1868-2 at 6–12 (discussing issues with Dr. Keyes methodology that existed in Track One, and continue to exist here, and citing cases in support of exclusion); ECF No. 2479 at 4–6 (same).[7]

The only articles Dr. Keyes reviewed concern marketing by drug manufacturers, not by any of the pharmacy chains in this case.[8] Indeed, during a *Frye* Hearing in New York, Dr. Keyes was asked to confirm that those identical articles[9] all pointed to defendants other than the chain pharmacies and major wholesale distributors, Dr. Keyes responded: "That's right." Ex. 6 at 149:10–15.[10] In her Track Three deposition, moreover, Dr. Keyes testified that she was not

[7] *See, e.g.*, *Nelson v. Tenn. Gas Pipeline Co.*, 243 F.3d 244, 254 (6th Cir. 2001); *In re Prempro Prods. Litig.*, MDL No. 4:03CV01507-BRW, 2012 WL 12906583, at *3 (E.D. Ark. Aug. 29, 2012); *In re Rezulin Prods. Liab. Litig.*, 309 F. Supp. 2d 531, 556 (S.D.N.Y. 2004); *In re Actos (Pioglitazone) Prods. Liab. Litig.*, No. 6:11-md-2299, 2014 WL 12653759, at *12 (W.D. La. Jan. 14, 2014).

[8] The articles also discuss association, not causation. *See*, *e.g.*, Exs. 12, 13, 15, 17, 20. This is true of the articles that Dr. Keyes cites related to opioid prescribing. For example, an article entitled "Association of Pharmaceutical Industry Marketing of Opioid Products to Physicians with Subsequent Opioid Prescribing," states: "Limitations include the possibility of reverse causality because physicians who receive industry payments may be predisposed to prescribe opioids. *Our findings establish an association, not cause and effect.*" Ex. 13 at 863.

[9] *Compare* Ex. 1 at nn.23–28 & 135–43 *with* Ex. 4 at nn.16–21 & 103–11. Dr. Keyes also relied on the same articles in Track Two, where, like in Track One, her opinions were excluded. Ex. 3 at nn.24–29 & 133–41. While Dr. Keyes cites four articles in addition to the articles that she cited in her Track One report, none of the new articles relate to prescription opioids, Exs. 17–20, and, on-their-face, they relate to manufacturers. *See*, *e.g.*, Ex. 17 at 684 ("Requests by physicians that drugs be added to a hospital formulary were strongly associated with the physicians' *interaction with the companies manufacturing the drugs*.") (emphasis added); Ex. 19 at 2 ("This paper presents empirical evidence that, although payments do raise expenditures *on a firm's product*, the quality of drugs prescribed does not fall and, in fact, appears to increase.") (emphasis added).

[10] Tellingly, in New York, where manufacturers were in the case (instead of severed, as they are here), both Dr. Keyes and Plaintiffs focused their discussion of marketing on the manufacturers. *See also, e.g.*, Ex. 6 at 104:24–105:5 (Q. What did Hadland find in this study? A. They found an association between the, the amount of money that doctors received from *opioid manufacturers* with subsequent opioid prescribing.") (emphasis added); *id.* at 105:19–25 (discussing how the study mentions Insys Therapeutics, Teva Pharmaceuticals, and Janssen Pharmaceuticals); *id.* at 107:6–9 (Q. Did you, in your work on this case, evaluate the marketing materials of any manufacturer Defendant? A. No."); *id.* at 264:10–12 ([Plaintiffs' Counsel]: "I'm not sure that was it. I was referring to marketing statements by the manufacturer Defendants.").

offering opinions about any specific company's marketing, and that she only had the expertise to discuss the companies specifically mentioned in the articles she cites in her report. Ex. 5 at 86:4–12, 88:16–89:18, 90:2–91:1. While those articles mention manufacturers,[11] none of them discuss Defendants. Exs. 10–20.[12]

If her sworn testimony was not enough to confirm that her opinions are directed at entities other than Defendants, Dr. Keyes' Track Three report does so: Before she offers her marketing causation assessment, Dr. Keyes states that she "did not evaluate the specific *marketing materials of manufacturers*," Ex. 1 at 33 (emphasis added); *see also* Ex. 7 at 478:14–479:6 (Q. Did you consider whether what physicians learned in medical school impacted their decision to write opioids? A. So I do epidemiological literature review and data analysis. It is at a population level. And the population level data indicates that often what physicians were told, they were misinformed about the risks and benefits of opioids. Q. And were they—who were they told by? A. The available literature that I have cited in this report points to materials that were received by [sic] the *manufacturers*.") (emphasis added).

At her Track Three deposition, however, Dr. Keyes seemed to backtrack on her earlier sworn testimony. She refused to acknowledge that the marketing opinions and articles that she cites in support of them relate to manufacturers, not Defendants. Instead, she maintained that her

[11] *See, e.g.*, Ex. 24 (discussing marketing by Purdue); Ex. 13 at 862 (identifying Insys, Teva, and Janssen as the three companies with the highest payment totals, and noting that the findings "suggest that manufacturers should consider a voluntary decrease or complete cessation of marketing to physicians")..

[12] In a section of her report that is separate from her marketing opinions, Dr. Keyes includes a quote from an article about "'aggressive and highly effective marketing tactics on the part of the pharmaceutical industry (manufacturers, distributors, and pharmacies).'" Ex. 1 at 40. That article does not mention any specific pharmacy. It also provides no analysis in support of that statement, except a discussion of Purdue's marketing. Lastly, in support of that statement, it cites one article, which was authored by, among others, several individuals serving as experts for various plaintiffs in the opioid litigation (Andrew Kolodony, Caleb Alexander, and David Courtwright). Ex. 22. That article, which also discusses marketing by Purdue, does not discuss marketing by pharmacies, or even include any of the following words: pharmacy, pharmacies, CVS, Walgreens, Walmart, Rite Aid, or Giant Eagle. *Id.*

marketing opinions and the articles she cites might apply to Defendants. They do not, and her refusal to acknowledge that fact only serves to further illustrate the unreliability of her methodology and her opinions, and demonstrate why they should be excluded as to Defendants.

First, while acknowledging that the articles that she cites in her report relate to marketing to physicians, Ex. 5 at 91:2–5, which is an activity that manufacturers engage in, Dr. Keyes testified that she could not recall whether the articles were discussing the marketing activities of manufacturers, *id.* at 76:13–23; 103:23–104:22.

Second, when shown an article that clearly related to marketing by manufacturers, Ex. 14, she dismissed it as unrelated to opioid marketing, Ex. 5 at 79:11–20. But she cites the article in her report, and she relies on it and other non-opioid marketing articles to support her marketing opinions. Ex. 1 at 33 & n.141. In her report, she incorrectly cites the article as related to the marketing of opioids. *See id.*

Third, when asked whether an article about marketing of prescription opioids related to manufacturers, she argued that the question constituted a "narrow interpretation of the data," Ex. 5 at 87:11–19, even though, as she acknowledged, the article specifically mentioned three manufacturers (Insys, Teva, and Janssen) and made a recommendation about manufacturer conduct, *id.* at 81:7–82:12. What is more, during a hearing in the New York case, which involved manufacturers, distributors, and the chain pharmacies, Dr. Keyes testified under oath that the article concerned manufacturer conduct:

> Q. What did Hadland find in this study?
>
> A. They found an association between the amount of money that doctors received from *opioid manufacturers* with subsequent opioid prescribing.

Ex. 6 at 104:25–105:5 (emphasis added). Moreover, Dr. Keyes was not, in fact, aware of any data that contradicted her earlier (correct) evaluation of the article; instead, she was speculating that the

term "pharmaceutical companies," as used in the article, might be read to include Defendants, Ex. 5 at 82:13–18.

Fourth, in a strained attempt to drag Defendants within the articles about opioid prescribing she cites, Dr. Keyes theorized that articles that relied on the Open Payments database for their analysis might apply to Defendants, even if they only discussed manufacturers, at least if the database also showed payments by Defendants.[13] Ex. 5 at 76:13–23, 82:13–25, 83:23–84:7, 84:19–85:7, 87:20–88:7, 103:23–105:23. But none of Defendants are listed in the Open Payments database. *See* https://openpaymentsdata.cms.gov/.

Any opinion Dr. Keyes could offer on the effects of marketing of prescription opioids by Defendants would be based on no published literature and no data. It would be the pure *ipse dixit* of an expert without any scientific foundation.

C. Dr. Keyes' Marketing Opinions Do Not "Fit" This Case.

This case is about whether conduct by specific Defendants caused a public nuisance in specific counties. Dr. Keyes' opinions, however, do not evaluate any specific Defendant's conduct, let alone any such conduct by a specific Defendant in Lake or Trumbull Counties. Ex. 5 at 26:23–28:8. It is well-settled that Plaintiffs cannot simply lump all Defendants together (including entities not even in the Track Three cases); they must show that "the conduct of *each* defendant was a substantial factor in producing the harm." *Pang. v. Minch*, 559 N.E.2d 1313, 1324 (Ohio 1990) (emphasis added). As discussed above, Dr. Keyes failed to evaluate whether

[13] "Open Payments is a national transparency program that collects and publishes information about financial relationships between the health care industry (i.e. drug and device companies) and providers (i.e. physicians and teaching hospitals). These relationships may involve payments to providers for things such as research, meals, travel, gifts, or speaking fees. One of the ways that the Centers for Medicare & Medicaid Services (CMS) provides data to the public is through this search tool, which allows the public to search for physicians and teaching hospitals receiving payments, as well as companies that have made payments." Ex. 23. The articles cited by Dr. Keyes that relate to opioid prescribing use those marketing related payments (e.g., payments for meals) to analyze whether marketing is associated with certain results (e.g., increased prescribing by doctors who receive the payments/marketing). Exs. K, M, N.

any Defendant engaged in any marketing and, if so, what type(s), what marketing materials were used, whether those materials were true or false, Ex. 5 at 26:3–28:8, 105:24–106:18, 91:19-92:18, or whether those materials affected any prescriber's behavior, let alone the behavior of any prescriber in Lake or Trumbull Counties, *id.* at 91:19–92:18. *See also* ECF Nos. 1868-2 at 8–12 & 2479 at 4–6 (discussing same issues in Track One).

D. Absent an Instruction that Dr. Keyes' Marketing Opinions Do Not Apply to Defendants, Those Opinions are Misleading, Confusing, and Unfairly Prejudicial

Here, allowing Dr. Keyes to suggest, on the core issue of causation, that Defendants engaged in marketing that changed the prescribing practices of physicians in Lake and Trumbull Counties (or anywhere for that matter) would be misleading, confusing, and unfairly prejudicial. An example from Dr. Keyes' deposition illustrates the danger. During her deposition, Dr. Keyes, with no basis to do so, theorized that a reference to "pharmaceutical companies" in an article that, as discussed above, referred to manufacturers, might be read to refer to Defendants. Ex. 5 at 82:13–18. Such speculation about causation by Dr. Keyes—or during summation by Plaintiffs' counsel—would be highly misleading, confusing, and unfairly prejudicial, and cannot be allowed to occur. *See Daubert*, 509 U.S. at 595 (recognizing the potential that "[e]xpert evidence can be both powerful and quite misleading," and the Court's role is to keep such misleading testimony from reaching the jury under Rules 702 and 403); *United States v. Geiger*, 303 F. App'x 327, 329 (6th Cir. 2008); *see also* ECF No. 1868-2 at 12 (discussing potential prejudice of allowing Dr. Keyes to testify about marketing causation).

II. DR. KEYES' OPINIONS ABOUT A CAUSAUL RELATIONSHIP BETWEEN PRESCRIPTION OPIOIDS AND SYNTHETIC OPIOID-RELATED HARMS SHOULD BE EXCLUDED.

A. Dr. Keyes Applies an Unsupported and Unreliable Methodology to Opine that Prescription Opioids Are Responsible for Harms Related to Illicit Synthetic Opioids.

Dr. Keyes' opinion that the use of prescription opioids is responsible for harms from illicit synthetic opioids rests on an unreliable methodology that does not survive scrutiny. In reaching her conclusions, Dr. Keyes did not consider confounding factors, alternative explanations, or present any of the kinds of analyses of a statistical association necessary to support the sort of inference of causation described in the Epidemiology chapter of the Federal Judicial Center, Reference Manual for Scientific Evidence at 566–71 (3d ed. 2011) (calculations of relative risk, odds ratio, or attributable risk); *id.* at 591 ("When researchers find an association between an agent and a disease, it is critical to determine whether the association is causal or the result of confounding."); *see also In re Lipitor (Atorvastatin Calcium) Mktg., Sales Pracs. and Prods. Liab. Litig.*, 174 F. Supp. 3d 911, 916 (D.S.C. 2016) ("In assessing causation, epidemiologists 'first look for alternative explanations for the associations, such as bias or confounding factors,' and then apply the Bradford Hill factors to determine whether an association reflects a truly causal relationship.") (citing the Reference Manual on Scientific Evidence at 598–600, and collecting cases).

Dr. Keyes layers unsound assumptions to conclude that prescription opioids caused harms from drug users ingesting illegal drugs adulterated with illicitly manufactured synthetic opioids by drug dealers, *id.* at 4 (opinion 8), 39, 59–61. This is unsound for several reasons.

First, Dr. Keyes cites survey data concerning percentages of people who have misused prescription opioids before using heroin. *Id.* at 39; *see also id.* at 36. But that data reflects only a

sequence of events, and is not even a theoretical basis for inferring causation.[14, 15] It is unsurprising that many heroin abusers previously abused other drugs, including prescription opioids, as a result of common physiological, psychological, and sociological influences, rather than because access to one drug causes abuse of another. *See, e.g.*, Ex. 1 at 11 (recognizing addiction is multi-factorial in its etiology); Ex. 24 at 9 (“”[W]e found that past-year illegal drug use other than NMUPO and alcohol use disorder were strongly associated with NMUPO-alone, MDE-alone and, particularly, comorbid NMUPO and MDE.”); Ex. 25 at e53 (“Many of the well-documented risk factors for illicit drug use predict both nonmedical prescription opioid use and other illicit drug use.”). Dr. Keyes also ignores, among other things, that those same individuals often use myriad other drugs before and after heroin; that addiction is multi-factorial;[16] and that there is often significant time,

[14] Ex. 1 at 36. For example, Dr. Keyes cites the Cicero study discussed in footnote 4, which looked at the percentage of individuals who used prescription opioids before heroin at various points in time. Ex. 26. She also cites a paper by Lankenau and others. Ex. 27. That study looked at drug use by 50 injection drug users “who had misused prescription drugs at least three times in the past three months.” *Id.* These individuals typically used other drugs before prescription opioids, and were poly-drug users. *Id.*; Ex. 5 at 145:6–149:1. The paper by Mateu-Gelabert and others that she cites noted that “[e]arly PO misuse was typically described as taking place within a normative peer context in which poly-drug and poly-pharmaceutical use was widely accepted,” and notes that its results should be “interpreted with caution in light of several limitations,” including “that they used “quantitative data to precisely characterize our data, not to make statistical inferences about larger populations.” Ex. 28. Other studies Dr. Keyes cites document different percentages; indeed, Dr. Keyes notes, in her report, that one shows 39.8% of heroin users used prescription opioids before heroin. Ex. 2 at 36.

[15] These percentages change over time too. For example, one of the studies that Dr. Keyes relies on for her 70% figure notes that: “Of those who began their opioid abuse in the 1960s, more than 80% indicated that they initiated their abuse with heroin. In a near complete reversal, 75% of those who began their opioid abuse in the 2000s reported that their first regular opioid was a prescription drug. Beginning in 2010 (2010–2013), these trajectories showed a shift in direction (ie, heroin use increased as the first opioid of abuse and prescription opioid use decreased.”. Ex. 26 at 823. In short, the percentages being used are not static. By 2010, before synthetic opioids were introduced into the drug supply, the trajectory had shifted direction. The data on which Dr. Keyes relies—which predates the introduction of synthetic opioids—likely overestimates the percentage of heroin users who misused prescription opioids before using heroin. Dr. Keyes 53.4% figure also uses data that only runs to 2014, and it represents “the proportion of heroin users who report non-medical prescription opioid use at an age equal to or prior to the age in which they began using heroin.” Ex. 1 at 61. Due to the inclusion of individuals heroin users who report non-medical prescription opioid use at an age equal to . . . the age in which they began using heroin,” it is quite possible that the percentage overestimates the individuals who misused prescription opioids before heroin (*i.e.*, it is quite plausible the sequence is heroin and then prescription opioids in the same year for at least some of the individuals).

[16] Ex. 1 at 11 (explaining that her “risk factor” framework will assess something as a “cause” if some “some cases would not have occurred in the absence of prescription opioid use” and that the “framework does not preclude or ignore that addiction and related harms are multi-factorial in their etiology”).

almost certainly involving varied and individualized trajectories, between prescription opioid use and heroin use.[17] None of the studies on which Dr. Keyes relies concludes that there is a causal relationship between prescription opioids and heroin, and they certainly do not posit that 70-80% of heroin use is "attributable" to prescription opioid use. *See* Ex. 29 at 15–16 (describing limitations of data, including that it was not intended "to make statistical inferences about larger populations," and "may not be generalizable to other locations or ages") Ex. 27 at 10 ("results may be biased toward IDUs who more frequently misused a range of prescription drugs, including opioids"); *see also, e.g.*, Exs. 26, 29–32; Ex. 6 at 165:18–169:7.

After improperly attributing a high percentage of heroin use to prescription opioid use, Dr. Keyes then leaps to blaming prescription opioids for deaths from the consumption of high potency synthetic opioids after drug dealers began adulterating the heroin supply.[18] But even if one were to accept Dr. Keyes' reasoning (and one should not), it is based on nothing more than the legally erroneous proposition that if heroin use is associated with prior use of prescription opioids, then

[17] *See, e.g.*, Ex. 27 at 4 (noting that opioid misuse "typically followed first use of alcohol, marijuana, and prescription stimulants and preceded initiation of harder drugs, such as cocaine, methamphetamine, and heroin" and opioid misuse occurred, on average, two years before heroin use); Ex. 30 at 14 ("Although the findings indicate that NMPR use is a common step on the pathway to heroin initiation, most NMPR users do not progress to heroin use. Second, heroin use appears to be neither a sufficient nor necessary condition for the subsequent onset of NMPR use. Put differently, it appears that there are many unique pathways leading to NMPR use, and many of those do not involve heroin as a developmental precursor, or milestone, on the career trajectory of an illicit drug user."); Ex. E at 130:5–138:24; Ex. 32 ("The mean time from first pharmaceutical opioid use to heroin use was 8.2 years . . . among heroin initiates. However, the rapidity of transition differed by history of methamphetamine use and reporting supply problems with obtaining pharmaceutical opioids."). A study that Dr. Keyes does not cite in her report notes: "The results of this study indicate that only 4% of those who experience their first opioid via a physician's prescription were truly drug naïve." Ex. 33. The study goes on to state that "nearly our entire sample had used alcohol, nicotine, and marijuana before their initial opioid prescription," that "70% had experience with other types of drugs," and that, on average, "four to five different types of drugs were used prior to initial opioid exposure from a prescription." *Id.* at 243. The article then suggests that "physicians and pain management specialists should routinely ask patients that are candidates for opioid treatment about all of their drug use, not simply smoking and alcohol use, which is generally the norm." *Id.* at 244. The lead author on that article Theodore J. Cicero, PhD, is also the lead article on the article discussed in Dr. Keyes' report, Ex. 26, that is quoted in footnote 4 about percentages of individuals who misuse prescription opioids before later using heroin.

[18] As discussed below, even if this attribution were grounded in science, it would be inadmissible because it would mislead the jury about the principles it should apply to find but for and direct causation, including the consideration of alternative and intervening causes.

so is any indirect consequence of heroin use; that is a legal, not a scientific question and should not be admitted as an expert opinion. Even if this were a scientific question, it is not supported by data or a reliable methodology. Dr. Keyes has not written about these opinions elsewhere and, in turn, has not subjected them to peer review. Dr. Keyes also does not purport to be an expert in the market for illicit drugs or the behavior of illicit drug buyers or sellers.[19] Moreover, in stark contrast to the rest of her report and her stated literature review methodology, Dr. Keyes cites no literature that concludes that prescription opioids are "responsible" for harms arising from illicit synthetic opioids. Nor could she. Prescription opioids have existed for a very long time and harms from illicit synthetic opioids are a relatively recent issue, *see, e.g.*, Ex. 1 at 39 & 45, which resulted from, as Dr. Keyes recognizes, drug dealers adulterating the illicit drug supply, *see, e.g.*, *id.* at 39 & 55, including non-opioid drugs (*e.g.*, cocaine, methamphetamine, and others) with illicit synthetic opioids. Harms arising from these recent—and unforeseeable illegal activities—were not caused by prescription opioids.

Moreover, while Dr. Keyes' "estimates" might be subject to testing and evaluation, she has not done so. For example, in Lake County in 2017, Dr. Keyes estimates that there were 64 opioid overdoses that did not involve prescription opioids; she estimates that 59 of those deaths involved synthetic opioids; using her 53.4% figure, she estimates that 34 (64 * 0.534 = 34.167) of those deaths were indirectly attributable to prescription opioids; and 31 of those would have involved synthetic opioids. Ex. 1 at 61; Ex. 33, Dr. Keyes report does not describe anything that she has done to evaluate whether those "estimates" are accurate for 2017 in Lake County, or in any other year.

[19] *Cf.* ECF No. 2549 (excluding Dr. Keyes' marketing opinions due to her lack of expertise in that area).

In other words, Dr. Keyes' opinions that prescription opioids are responsible for harms caused by illicit synthetic opioids, or that harms are attributable to or caused by prescription opioids, rely solely on her say-so. They are not the product of a sound and reliable methodology. No matter how well-credentialed the expert, courts do not admit opinions that are nothing more than an expert's "*ipse dixit*." *Nelson*, 243 F.3d at 254. Dr. Keyes' opinions should be excluded.

III. DR. KEYES' OPINIONS ATTRIBUTING RESPONSIBILITY FOR SYNTHETIC OPIOID-RELATED HARMS TO PRESCRIPTION OPIOIDS ILLUSTRATE THAT HER CAUSAL ANALYSIS IS HIGHLY MISLEADING, CONFUSING, AND UNFAIRLY PREJUDICIAL, AND SUCH TESTIMONY SHOULD BE PRECLUDED OR FOLLOWED BY A LIMITING INSTRUCTION.

Dr. Keyes should not be allowed to mislead and confuse the jury by offering opinions on jury questions of causation (or what will appear to be opinions on causation), causing unfair prejudice to Defendants. Dr. Keyes states that she ascribes a causal relationship between prescription opioids and "opioid use disorders, overdoses, and related harm if some cases would not have occurred in the absence of prescription opioids use." Ex. 1 at 11. And, throughout her report, she draws a causal relationship between various things, like prescription opioids and heroin. Putting aside, for the moment, that her analysis is flawed in a variety of ways from an epidemiological standpoint (as the discussion in Section II above demonstrates), her definition of causation differs in significant and important ways from legal causation. Her opinions that blame prescription opioids for causing harms from illicit synthetic opioids illustrate the dangers—and why such testimony must be excluded or followed by a limited with an instruction—because it will mislead and confuse the jury, and unfairly prejudice Defendants.

Dr. Keyes claims that prescription opioids are "responsible" for harms from illicit synthetic opioids, that 70–80% of fentanyl-related opioid deaths are "attributable" to prescription opioids, and that "a minimum of 53.4% of [opioid] deaths are indirectly due to prescription opioids," if presented to the jury, would risk creating the false impression that Dr. Keyes has concluded that

Defendants were the *legal* cause of a public nuisance. But that question is one for the jury, not for Plaintiffs' expert, and the only instruction the jury should receive on causation should come from the Court.

The abolition of the "ultimate issue" prohibition in Federal Rule of Evidence 704 "does not lower the bar so as to admit all opinions. Under Rules 701 and 702, opinions must be helpful to the trier of fact, and Rule 403 provides for exclusion of evidence which wastes time. These provisions afford ample assurances against the admission of opinions which would merely tell the jury what result to reach . . . . McCormick § 12." Fed R. Evid. 704 advisory comm. note. "[T]estimony offering nothing more than a legal conclusion—i.e., testimony that does little more than tell the jury what result to reach—is properly excludable under the Rules. It is also appropriate to exclude "ultimate issue" testimony on the ground that it would not be helpful to the trier of fact when "'*the terms used by the witness have a separate, distinct and specialized meaning in the law different from that present in the vernacular*.'" *Woods v. Lecureux*, 110 F.3d 1215, 1220 (6th Cir. 1997) (citing *United States v. Sheffey*, 57 F.3d 1419, 1426 (6th Cir. 1995) (emphasis in *Sheffey*)).

Here, the problem is not a conflict between a legal definition and "the vernacular," but between legal principles governing causation and an epidemiologist's "attribution"—even if Dr. Keyes were correctly applying epidemiological standards (which she is not, as explained above). Expert opinion testimony must be helpful to the jury, but "[h]elpful opinions do not "merely tell the jury what result to reach." *Youngberg v. McKeough*, 534 F. App'x 471, 479 (6th Cir. 2013) (quoting *McGowan v. Cooper Indus., Inc.*, 863 F.2d 1266, 1272 (6th Cir. 1988) (quoting Fed. R. Evid. 704 advisory comm. note (1972 Proposed Rules)). The words "responsible," "attributable," or "indirectly due to" convey a causal relationship. *See, e.g.*, Ex. 1 at 59 (arguing that prescription opioid use is "causally associated" with "heroin and other opioid use"). It would be especially

misleading and prejudicial to state that 70-80% of fentanyl-related opioid deaths are "attributable" to prescription opioids, or that "a minimum of 53.4% of [opioid] deaths are indirectly due to prescription opioids." As discussed above, Dr. Keyes lacks sound support to blame prescription opioids for the harms caused by drug dealers' recent introduction of illicit synthetic opioids into the illegal drug supply of heroin, methamphetamine, cocaine, and other drugs. Moreover, the scenario she discusses does not approach the legal standard for causation, but her terminology conveys, without proof, that a causal relationship exists. Therefore, Dr. Keyes' opinions and testimony on the purported relationship between prescription opioids and harms from illegal synthetic opioids would be misleading and confusing to the jury, and unfairly prejudicial to Defendants.

CONCLUSION

For the reasons explained above, this Court should exclude: (a) Dr. Keyes' testimony and opinions marketing opinions as to Defendants; and (b) Dr. Keyes' testimony and opinions that prescription opioids are responsible for synthetic opioids or harms arising from them. This Court should also exclude or provide a curative limiting instruction regarding Dr. Keyes' opinions and testimony about responsibility, attribution, causation, because such testimony will be misleading, confusing, and unfairly prejudicial.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I, the undersigned, hereby certify that the foregoing document was served via email to all counsel of record on July 23, 2021.

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